Published in final edited form as:

Pancreas. 2013 July ; 42(5): 836–840. doi:10.1097/MPA.0b013e318279f720.

Variation in the Gamma-Glutamyltransferase 1 (*GGT1*) Gene and Risk of Chronic Pancreatitis

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Abstract

Objective—Individuals with chronic pancreatitis are at increased risk for pancreatic cancer. We hypothesized that genetic variation in the gamma-glutamyltransferase 1 (*GGT1*) gene, which was recently reported associated with pancreatic cancer risk in a genome-wide association study, is also associated with risk of chronic pancreatitis.

Methods—Associations between common polymorphisms in *GGT1* and chronic pancreatitis were evaluated using data and samples from the North American Pancreatitis Study 2. Cases ($N=496$) and controls ($N=465$) were genotyped for four single nucleotide polymorphisms (SNPs): rs4820599, rs2017869, rs8135987, and rs5751901. Odds ratios (OR) and corresponding 95% confidence intervals (95%CI) for chronic pancreatitis risk were calculated using multiple logistic regression models. Interactions with cigarette smoking and alcohol use were explored.

Results—SNPs rs8135987 and rs4820599 were both statistically significantly associated with risk of chronic pancreatitis; compared to common allele homozygotes, individuals with at least one minor allele were at increased risk (rs8135987, OR: 1.36, 95%CI: 1.03-1.80, P_{trend} : 0.01; rs4820599, OR: 1.39, 95%CI: 1.04-1.84, P_{trend} : 0.0; adjusted for age, sex, race, smoking status, and alcohol use). No significant interactions with cigarette smoking and alcohol use were observed.

Conclusion—Our results suggest that common variation in the *GGT1* gene may also affect risk of chronic pancreatitis.

Keywords

pancreatic cancer; chronic pancreatitis; case-control; SNPs; *GGT1*

Introduction

Chronic pancreatitis is an inflammatory condition that results in the destruction of the pancreas by irreversible scarring and fibrosis. Individuals with chronic pancreatitis are at

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Conflicts of Interest:

No conflicts of interest are reported.

increased risk for pancreatic cancer; a recent meta-analysis reported a relative risk of 13.3 [95% confidence interval (95% CI): 6.1-28.9].¹ The exact mechanism that links the two diseases is currently unknown. The association might be caused by a shared exposure to risk factors such as cigarette smoking and alcohol consumption, shared genetic susceptibility factors, and/or facilitation of tumor initiation and promotion by inflammation.²

In a two-stage genome-wide association study (GWAS) of pancreatic cancer recently conducted by our group, the strongest association with pancreatic cancer risk was observed for single nucleotide polymorphism (SNP) rs4820599 located in the gamma-glutamyltransferase 1 (*GGT1*) gene on chromosome 22q11.23.³ Fine-mapping results supported a role for this region in pancreatic carcinogenesis. *GGT1* encodes for the membrane-bound enzyme gamma-glutamyltransferase (GGT) which is highly expressed in tissues with secretory or absorptive functions such as liver and pancreas. GGT plays a key role in maintaining intracellular glutathione levels which are critical for phase II reactions and the detoxification of reactive metabolites and xenobiotics, and is a marker of oxidative stress.⁴ GGT levels are clinically mostly used as a marker for alcohol abuse and liver function but have also been reported associated with various diseases, including cardiovascular disease and cancer.⁵⁻⁸ Furthermore, polymorphisms in the glutathione pathway have been found associated with risk of developing both acute and chronic pancreatitis.^{9,10}

Despite the strong link between chronic pancreatitis and pancreatic cancer, only approximately 5% of those with chronic pancreatitis will develop pancreatic cancer.¹ Therefore, screening of chronic pancreatic patients for pancreatic cancer is currently not recommended. Enhanced knowledge of the mechanism that links the two diseases may result in the ability to effectively identify those chronic pancreatitis patients who are at a high enough risk to warrant pancreatic cancer surveillance. We hypothesized that genetic variation in *GGT1* is also associated with an increased risk of chronic pancreatitis. To test our hypothesis, we evaluated associations between polymorphisms in *GGT1* and chronic pancreatitis using data and samples from the North American Pancreatitis Study 2 (NAPS2). Interactions between SNPs and cigarette smoking status and alcohol use were also explored. Results are reported in this manuscript. To our knowledge, this is the first study to evaluate the relationship between genetic variation in *GGT1* and risk of chronic pancreatitis.

Material and Methods

Study Population

Cases and controls were NAPS2 study participants. Details of NAPS2 have been described elsewhere.^{11,12} Briefly, the NAPS2 is a multicenter consortium of 20 US centers that prospectively enrolled 1000 pancreatitis patients (540 chronic pancreatitis and 460 recurrent acute pancreatitis patients) and 695 controls between August 2000 and September 2006. Written informed consent was obtained from all participants and the study was approved by the Institutional Review Boards at each participating center. Study participants completed a self-administered questionnaire that included questions on medical history, family history, and dietary and lifestyle factors (including alcohol and tobacco use), and the majority provided a blood sample. Chronic pancreatitis was confirmed by imaging studies. Study participants were classified by drinking status based on self-reported alcohol consumption: abstainer (no alcohol consumption or <20 drinks in lifetime), light drinkers (0.5 drinks per day or 3 drinks per week), moderate drinkers (>0.5 to 1 drink per day or 4 to 7 drinks per week for women; >0.5 to 2 drinks per day or 4 to 14 drinks per week for men), heavy drinkers (>1 to <5 drinks per day or 8 to 34 drinks per week for women; >2 to <5 drinks per day or 15 to 34 drinks per week for men), and very heavy drinkers (5 drinks per day or 35 drinks per week for both sexes).¹¹ Smoking status was classified as never (smoked 100

cigarettes in lifetime), former and current smokers (both former and current smokers smoked >100 cigarettes). For the current study, only cases 18 years of age or older with chronic pancreatitis ($N=525$) and unrelated controls ($N=479$) were included.

DNA extraction and Genotyping

Genomic DNA was extracted from buffy coat samples using the Qiagen FlexiGene DNA Kit (Qiagen Inc., Valencia, Calif., USA). Cases and controls were genotyped for in total four SNPs in *GGT1*: rs4820599, rs2017869 and rs8135987 were included because they were found to be associated with pancreatic cancer in our previous study³; rs5751901 was included because it has been reported associated with increased GGT serum levels.¹³ Genotyping was conducted at the University of Pittsburgh Genomics and Proteomics Core Laboratories using MassARRAY® iPLEX Gold (Sequenom, Inc., San Diego, CA). To monitor genotyping quality, a control DNA sample and a DNA-free ('negative') control were included, in duplicate, on every plate. No discrepant genotypes were detected. Genotype data was not available for 29 cases and 14 controls, leaving a final number of 496 cases and 465 controls for analysis. Among those included in the analysis, call rates for the four SNPs were: rs4820599 – 99.7%, rs2017869 – 99.9%, rs8135987 – 98.6%, and rs5751901 – 99.2%.

Statistical Analysis

Differences in characteristics between cases and controls were assessed using *t*-tests for continuous variables and Chi-square tests for categorical variables. Deviation from Hardy-Weinberg Equilibrium was evaluated in the control population with the Chi-square goodness-of-fit test. Odds ratios (OR) for chronic pancreatitis risk and corresponding 95% CIs were calculated using multiple logistic regression models. Linear trend was assessed using numerical scores assigned to the ordered categories (0 to the first category, 1 to the second, etc.) as continuous variable in the model. Both additive and dominant genetic models were evaluated. Common allele homozygotes were used as reference group. Analyses were adjusted for age (continuous), sex (male, female), race (white, other), cigarette smoking status (never, former, current), and alcohol use (never, ever). Effect modification by the different SNPs was explored for the association of both cigarette smoking and alcohol intake with risk of chronic pancreatitis. Log-likelihood ratio tests were calculated to test for statistical significance of multiplicative interactions. All significance tests were two-sided; *P* values <0.05 were considered statistically significant. All analyses were performed with use of the SAS® statistical software package (SAS version 9.2, SAS Institute Inc., Cary, NC).

Results

Characteristics of the study population are presented in Table 1. Cases were significantly younger than controls, more often male, current smokers and very heavy drinkers. The frequency of white participants was similar among cases and controls. All four SNPs were in Hardy-Weinberg Equilibrium (data not shown). The heterozygote and rare allele homozygote genotypes for SNP rs8135987 were significantly more common among cases than controls (Table 1).

Cigarette smoking was, as expected, significantly associated with risk of chronic pancreatitis in our study population (ever versus never: OR: 3.07, 95% CI: 2.28-4.14; adjusted for age, sex, race and alcohol use). Current smokers had the highest risk (former versus never: OR: 1.69, 95% CI: 1.18-2.41; current versus never: OR: 5.03, 95% CI: 3.55-7.14; *P*trend=<.0001). Ever use of alcohol was not significantly associated with risk of chronic pancreatitis after adjustment for age, sex, race and smoking status (data not shown). However, compared

to never drinkers, those that drink very heavily (5 drinks per day or 35 drinks per week) had a significantly increased risk (OR: 2.36, 95% CI: 1.34-4.14; $P_{\text{trend}}=0.01$; adjusted for age, sex, race and smoking status).

Table 2 shows results of case-control comparisons, both unadjusted and adjusted, conducted to assess main effects of the different genotypes on chronic pancreatitis risk. Compared to rs8135987 common allele homozygotes, individuals with at least one minor allele of this SNP had a statistically significantly increased risk of chronic pancreatitis. Similarly, individuals with at least one minor allele of SNP rs4820599 had a statistically significantly increased risk of chronic pancreatitis compared to common allele homozygotes. Borderline significant associations were observed for the two other SNPs. When repeating analyses among whites only, similar results were observed though results were no longer significant (data not shown).

We subsequently explored whether the different genetic variants modified the relationship between cigarette smoking and risk of chronic pancreatitis. To see the joint effect of genotype and smoking status on risk of chronic pancreatitis more clearly, a single reference group (never smoking common allele homozygotes) was used. Results are shown in Table 3. No significant interactions were observed. However, for all four evaluated SNPs, ever smokers with at least one rare allele were at highest risk. We similarly explored interactions between the four SNPs and alcohol use (reference group: never alcohol using common allele homozygotes) (Table 4). Results for very heavy alcohol users only versus never alcohol users are also shown in Table 4. No significant interactions were observed with alcohol use either.

Discussion

The results of this study implicate genetic variation in the *GGT1* gene as a potential risk factor for chronic pancreatitis. Utilizing samples and data from NAPS2, we evaluated associations between four common genetic variants in *GGT1* and risk of chronic pancreatitis. The SNPs that were investigated had previously been reported associated with either risk of pancreatic cancer or increased serum GGT levels. SNPs rs8135987 and rs4820599 were both statistically significantly associated with chronic pancreatitis risk in our study population. These two SNPs are in weak linkage disequilibrium (LD) with each other ($r^2=0.29$). We observed no statistically significant interactions between the evaluated SNPs and smoking status or alcohol use, suggesting that the effect of these two known risk factors for chronic pancreatitis is not modified by these polymorphisms.

To our knowledge, identification of shared genetic susceptibility factors has not been previously reported for chronic pancreatitis and pancreatic cancer. The largest pancreatic cancer GWAS to date, conducted by the PanScan consortium, observed the strongest association with pancreatic cancer risk for SNP rs505922 located in the ABO locus.¹⁴ This SNP was not found significantly associated with risk of chronic pancreatitis in the NAPS2 study population.¹⁵

GGT, the enzyme encoded by *GGT1*, enables glutathione catabolism by hydrolyzing the gamma-glutamyl bond between glutamate and cysteine and so is critical in maintaining intracellular glutathione levels, which protect cells against damage due to free radicals and oxidation.⁴ Oxidative stress can lead to pancreatic disease by both directly damaging pancreatic cells as well as activating pro-inflammatory signaling pathways.¹⁶ A recent study showed that antioxidant treatment in patients with chronic pancreatitis was effective in both relieving pain and reducing levels of oxidative stress.¹⁷ In addition to its role in glutathione metabolism, GGT also has the capability of hydrolyzing leukotriene C and prostaglandins,

which are lipid mediators involved in a variety of biological functions including inflammation and pain.^{18,19} Thus, functionally relevant polymorphisms in *GGT1* may well affect risk of developing chronic pancreatitis.

SNP rs8135987 is located in an intronic region of *GGT1* and within 2 kb of exon 9. This exon is crucial for substrate binding and catalysis,²⁰ Rs8135987 was originally selected as a tag SNP in our previous study,³ and there is currently no indication that it is functionally relevant. Instead, rs8135987 is likely in high LD with the actual causal SNP(s). SNP rs4820599 is located in the first intron of *GGT1*'s largest transcript (NM_013430.2), but *GGT1* has 3 other transcripts (NM_001032365.2, NM_005265.2, and NM_001032364.2) in which it is actually located in the promoter region (NCBI gene: www.ncbi.nlm.nih.gov/gene; accessed 8/21/2012). A quantitative trait loci study focusing on plasma liver enzyme levels found that rs4820599 was significantly associated with plasma GGT levels.²¹ This is consistent with results reported by Melzer et al.¹³ who found that SNP rs5751901, which is in high LD with rs4820599, was associated with GGT levels. The relationship between rs5751901 and risk of chronic pancreatitis was of borderline significance in our study. Unfortunately, information on GGT levels was not available for our study participants. The SNP function predictor FuncPred²² (<http://snpinfo.niehs.nih.gov/snpinfo/snpfunc.htm>; accessed 8/21/2012) predicts that rs4820599 is at a potential transcription factor binding site (TFBS). Variation within a TFBS can result in differential gene transcription which may explain the observed association of rs4820599 with risk of chronic pancreatitis. However, further research is required to confirm this.

Cigarette smoking and alcohol use are known risk factors for chronic pancreatitis and were associated with chronic pancreatitis risk in this study. Also, they can both increase oxidative stress in the pancreas.²³ Given GGT's critical role in maintaining glutathione levels, functional polymorphisms in *GGT1* may well alter an individual's exposure to reactive metabolites from cigarette smoke and alcohol consumption and so affect risk in developing chronic pancreatitis. However, no significant interaction with cigarette smoking or alcohol use was observed in our study population. This could in part be due to lack of power. Our study population was of medium size and it is possible that some associations and/or interactions were not detected due to insufficient power. In addition, although the evaluated SNPs had either been previously found associated with pancreatic cancer risk or GGT levels, it is possible that associations and/or interactions were not identified due to the limited number of SNPs investigated.

The strengths of our study include the availability of information on potential confounders such as age and alcohol and tobacco use, and the fact that diagnosis of chronic pancreatitis was confirmed by imaging studies. We did rely on self-reports of cigarette smoking and alcohol consumption and misclassification may have occurred.

In summary, our results suggest that SNPs rs8135987 and rs4820599 in *GGT1* affect risk of developing chronic pancreatitis and provide further insight into the genetic risk factors associated with this disease. If confirmed by other studies, the observed statistically significant associations support the hypothesis that pancreatic cancer and chronic pancreatitis share genetic susceptibility factors. Additional research is needed to evaluate clinical relevance. Eventually, elucidation of the mechanisms that link chronic pancreatic and pancreatic cancer may not only result in the ability to identify individuals at increased risk but may also prove useful for the development of effective intervention strategies.

Acknowledgments

Source of Funding: This research was funded in part by National Institutes of Health grants R25 CA057703, P30 CA047904, and R01 DK061451.

References

1. Raimondi S, Lowenfels AB, Morselli-Labate AM, et al. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. *Best practice & research Clinical gastroenterology*. Jun; 2010 24(3):349–358. [PubMed: 20510834]
2. Whitcomb DC. Inflammation and Cancer V. Chronic pancreatitis and pancreatic cancer. *American journal of physiology. Gastrointestinal and liver physiology*. Aug; 2004 287(2):G315–319. [PubMed: 15246966]
3. Diergaarde B, Brand R, Lamb J, et al. Pooling-based genome-wide association study implicates gamma-glutamyltransferase 1 (GGT1) gene in pancreatic carcinogenesis. *Pancreatology*. 2010; 10(2-3):194–200. [PubMed: 20484958]
4. Whitfield JB. Gamma glutamyl transferase. *Critical reviews in clinical laboratory sciences*. Aug; 2001 38(4):263–355. [PubMed: 11563810]
5. Targher G. Elevated serum gamma-glutamyltransferase activity is associated with increased risk of mortality, incident type 2 diabetes, cardiovascular events, chronic kidney disease and cancer - a narrative review. *Clinical chemistry and laboratory medicine : CCLM / FESCC*. Feb; 2010 48(2): 147–157. [PubMed: 19943812]
6. Strasak AM, Rapp K, Brant LJ, et al. Association of gamma-glutamyltransferase and risk of cancer incidence in men: a prospective study. *Cancer research*. May 15; 2008 68(10):3970–3977. [PubMed: 18483283]
7. Strasak AM, Pfeiffer RM, Klenk J, et al. Prospective study of the association of gamma-glutamyltransferase with cancer incidence in women. *International journal of cancer. Journal international du cancer*. Oct 15; 2008 123(8):1902–1906. [PubMed: 18688855]
8. Van Hemelrijck M, Jassem W, Walldius G, et al. Gamma-glutamyltransferase and risk of cancer in a cohort of 545,460 persons - the Swedish AMORIS study. *Eur J Cancer*. Sep; 2011 47(13):2033–2041. [PubMed: 21486691]
9. Verlaan M, te Morsche RH, Roelofs HM, et al. Glutathione S-transferase Mu null genotype affords protection against alcohol induced chronic pancreatitis. *American journal of medical genetics. Part A*. Jul 1; 2003 120A(1):34–39. [PubMed: 12794689]
10. Rahman SH, Ibrahim K, Larvin M, et al. Association of antioxidant enzyme gene polymorphisms and glutathione status with severe acute pancreatitis. *Gastroenterology*. May; 2004 126(5):1312–1322. [PubMed: 15131792]
11. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Archives of internal medicine*. Jun 8; 2009 169(11):1035–1045. [PubMed: 19506173]
12. Whitcomb DC, Yadav D, Adam S, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). *Pancreatology*. 2008; 8(4-5):520–531. [PubMed: 18765957]
13. Melzer D, Perry JR, Hernandez D, et al. A genome-wide association study identifies protein quantitative trait loci (pQTLs). *PLoS Genet*. May.2008 4(5):e1000072. [PubMed: 18464913]
14. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. *Nat Genet*. Sep; 2009 41(9):986–990. [PubMed: 19648918]
15. Greer JB, LaRusch J, Brand RE, et al. ABO blood group and chronic pancreatitis risk in the NAPS2 cohort. *Pancreas*. Nov; 2011 40(8):1188–1194. [PubMed: 21792085]
16. Leung PS, Chan YC. Role of oxidative stress in pancreatic inflammation. *Antioxidants & redox signaling*. Jan; 2009 11(1):135–165. [PubMed: 18837654]
17. Bhardwaj P, Garg PK, Maulik SK, et al. A randomized controlled trial of antioxidant supplementation for pain relief in patients with chronic pancreatitis. *Gastroenterology*. Jan; 2009 136(1):149–159. e142. [PubMed: 18952082]
18. Ikeda Y, Taniguchi N. Gene expression of gamma-glutamyltranspeptidase. *Methods Enzymol*. 2005; 401:408–425. [PubMed: 16399400]
19. Funk CD. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science*. Nov 30; 2001 294(5548):1871–1875. [PubMed: 11729303]

20. Ikeda Y, Fujii J, Taniguchi N. Significance of Arg-107 and Glu-108 in the catalytic mechanism of human gamma-glutamyl transpeptidase. Identification by site-directed mutagenesis. *The Journal of biological chemistry*. Feb 25; 1993 268(6):3980–3985. [PubMed: 8095045]
21. Yuan X, Waterworth D, Perry JR, et al. Population-based genome-wide association studies reveal six loci influencing plasma levels of liver enzymes. *Am J Hum Genet*. Oct; 2008 83(4):520–528. [PubMed: 18940312]
22. Xu Z, Taylor JA. SNPinfo: integrating GWAS and candidate gene information into functional SNP selection for genetic association studies. *Nucleic acids research*. Jul; 2009 37(Web Server issue):W600–605. [PubMed: 19417063]
23. Tandon RK, Garg PK. Oxidative stress in chronic pancreatitis: pathophysiological relevance and management. *Antioxidants & redox signaling*. Nov 15; 2011 15(10):2757–2766. [PubMed: 21902596]

Abbreviations used

CI	confidence interval
GGT	gamma-glutamyltransferase
GWAS	genome-wide association study
NAPS2	North American Pancreatitis Study 2
OR	odds ratio
SNP	single nucleotide polymorphism
TFBS	transcription factor binding site

Table 1

Characteristics of the Study Population

	Cases ($N_{\text{total}}=496$)	Controls ($N_{\text{total}}=465$)	<i>P</i>
Age (in years; mean $\pm$ sd)	50.7 $\pm$ 14.8	53.3 $\pm$ 15.1	0.01
Sex [women; $N(\%)$]	234 (47.2)	289 (62.2)	<0.0001
Race [white; $N(\%)$] ^a	422 (85.3)	405 (87.3)	0.36
Smoking Status [$N(\%)$] ^b			<0.0001
• Never	131 (26.5)	231 (50.4)	
• Former	122 (24.7)	140 (30.6)	
• Current	241 (48.8)	87 (19.0)	
Alcohol Use [$N(\%)$] ^c			0.03
• Never	131 (26.5)	125 (28.3)	
• Ever	388 (73.5)	334 (71.7)	
Alcohol Use [$N(\%)$] ^c			<0.0001
• Never	105 (21.3)	125 (28.3)	
• Light	93 (18.9)	134 (30.3)	
• Moderate	103 (20.9)	103 (23.3)	
• Heavy	64 (13.0)	54 (12.2)	
• Very heavy	128 (26.0)	26 (5.9)	
Genotype data [$N(\%)$]			
rs8135987			0.048
TT	198 (40.5)	216 (47.1)	
CT	228 (46.6)	202 (44.0)	
CC	63 (12.9)	41 (8.9)	
rs4820599			0.18
AA	218 (44.1)	232 (50.0)	
AG	208 (42.1)	178 (38.4)	
GG	68 (13.8)	54 (11.6)	
rs5751901			0.36
TT	190 (38.6)	194 (42.1)	
CT	236 (48.0)	217 (47.1)	
CC	66 (13.4)	50 (10.9)	
rs2017869			0.32
GG	172 (34.8)	175 (37.6)	
CG	229 (46.3)	218 (46.9)	
CC	94 (19.0)	72 (15.5)	

^aRace – $N=2$ missing data (1 case and 1 control)

^bSmoking status – $N=9$ missing data (2 cases and 7 controls)

^cAlcohol use – $N=26$ missing data (3 cases and 23 controls)

Table 2

Genetic Variation in *GGT1* and Risk of Chronic Pancreatitis

SNP ID	Genotype	Cases N (%)	Controls N (%)	OR (95% CI)	P _{trend}	OR (95% CI) ^a	P _{trend} ^a
rs8135987	TT	198 (40.5)	216 (47.1)	1.0 (ref.)	0.01	1.0 (ref.)	0.01
	CT or CC	291 (59.5)	243 (52.9)	1.31 (1.01-1.69)		1.36 (1.03-1.80)	
rs4820599	AA	218 (44.1)	232 (50.0)	1.0 (ref.)	0.07	1.0 (ref.)	0.03
	AG or GG	276 (55.9)	232 (50.0)	1.27 (0.98-1.63)		1.39 (1.04-1.84)	
rs5751901	TT	190 (38.6)	194 (42.1)	1.0 (ref.)	0.16	1.0 (ref.)	0.11
	CT or CC	302 (61.4)	267 (57.9)	1.16 (0.89-1.50)		1.22 (0.92-1.61)	
rs2017869	GG	172 (34.8)	175 (37.6)	1.0 (ref.)	0.16	1.0 (ref.)	0.10
	CG or CC	323 (65.3)	290 (62.4)	1.13 (0.87-1.48)		1.21 (0.90-1.61)	

^a Adjusted for age (continuous), sex (male, female), race (white, other), smoking status (never, former, current), and alcohol use (never, ever).

Table 3Smoking Status, Genetic Variation in *GGT1*, and Risk of Chronic Pancreatitis

	Smoking Status			
	Never Smokers		Ever Smokers	
SNP -Genotype	Cases/Controls	OR (95% CI) ^a	Cases/Controls	OR (95% CI) ^a
rs8135987				
TT	51/106	1.0 (ref.)	146/109	3.07 (1.98-4.76)
CT or CC	78/122	1.35 (0.86-2.13)	212/115	4.14 (2.70-6.34)
<i>P</i>interaction =0.73				
rs4820599				
AA	55/107	1.0 (ref.)	163/124	2.80 (1.83-4.29)
AG or GG	76/123	1.23 (0.78-1.92)	198/103	4.07 (2.65-6.25)
<i>P</i>interaction =0.12				
rs5751901				
TT	47/94	1.0 (ref.)	142/100	3.18 (2.00-5.05)
CT or CC	83/136	1.26 (0.80-2.00)	218/124	3.89 (2.51-6.03)
<i>P</i>interaction =0.58				
rs2017869				
GG	42/80	1.0 (ref.)	130/95	2.78 (1.72-4.49)
CG or CC	89/158	1.08 (0.67-1.74)	232/132	3.52 (2.24-5.53)
<i>P</i>interaction =0.22				

^aAdjusted for age (continuous), sex (male, female), race (white, other) and alcohol use (never, ever)

Table 4

Alcohol Use, Genetic Variation in *GGT1*, and Risk of Chronic Pancreatitis

SNP – Genotype	Alcohol Use					
	Never		Ever		Very Heavy	
	Cases/Controls	OR (95% CI) ^a	Cases/Controls	OR (95% CI) ^a	Cases/Controls	OR (95% CI) ^a
rs8135987						
TT	35/50	1.0 (ref.)	160/163	0.80 (0.47-1.37)	49/8	3.54 (1.31-9.61)
CT or CC	67/72	1.49 (0.84-2.65)	224/168	1.06 (0.63-1.78)	77/18	2.20 (0.94-5.14)
<i>P</i> _{interaction} = 0.82						
rs4820599						
AA	46/51	1.0 (ref.)	169/178	0.60 (0.36-0.98)	57/13	1.99 (0.84-4.74)
AG or GG	59/74	1.03 (0.59-1.81)	217/155	0.91 (0.56-1.49)	69/13	2.20 (0.92-5.24)
<i>P</i> _{interaction} = 0.44						
rs5751901						
TT	34/44	1.0 (ref.)	153/146	0.76 (0.44-1.31)	49/9	2.41 (0.90-6.48)
CT or CC	70/79	1.28 (0.72-2.29)	232/186	0.91 (0.54-1.55)	78/17	2.23 (0.97-5.13)
<i>P</i> _{interaction} = 0.54						
rs2017869						
GG	30/36	1.0 (ref.)	140/136	0.67 (0.38-1.21)	43/8	2.31 (0.82-6.50)
CG or CC	75/89	1.08 (0.59-1.98)	247/198	0.84 (0.48-1.47)	84/18	2.08 (0.89-4.90)
<i>P</i> _{interaction} = 0.94						

^a Adjusted for age (continuous), sex (male, female), race (white, other) and smoking status (never, former, current)